Measurement variations of MRI and CT in the assessment of tumor depth of invasion in oral cancer: A retrospective study

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Abstract: Purpose In oral squamous cell carcinoma (OSCC), depth of invasion (DOI) is an important predictive, prognostic, and staging parameter. While it is known that DOI can be estimated from preoperative imaging, an analysis of measurements variations according to imaging modality and to depth of tumor itself is lacking. The aim of the study was to assess the accuracy of imaging-based estimation of DOI in relation with the tumor histological DOI. Methods We retrospectively reviewed 121 patients with OSCC treated at University Hospital Zurich. The radiologic DOI of CT, T1-weighted, and T2-weighted MRI were compared with histological DOI. Frequency of relevant imaging artifacts was assessed as well. Results A total of 110 CT (90.9 %) and 90 MRI (74 %) were analyzed. Both modalities were available for 79 patients (65.3 %). The median histological depth of invasion was 9 mm (IQR 4.5–14). The median depth of invasion was 14 mm (IQR 10–20) on CT, 13 mm (IQR 8.25–18) on T1-weighted MRI, and 13 mm (IQR 9–18.75) on T2-weighted MRI. All diagnostic modalities tended towards an overestimation of the histopathologic DOI from about 5–15 %. This trend was most pronounced for thin tumors, for which both CT and MRI lead to upstaging in over 50 % of the cases. For 25 (22.7 %) patients, dental scattering on CT rendered DOI not estimable. For MRI, 18 patients (20 %) had artifacts (blooming, motion artifacts) rendering DOI not estimable. Conclusion CT and MRI measurements of DOI in OSCC lead to an overestimation of histological DOI, especially in tumors with DOI<5 mm, with upstaging by imaging in over 50 % of the cases. Artifacts were present in more than 20 % of performed images.

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Measurement variations of MRI and CT in the assessment of tumor depth of invasion in oral cancer: A retrospective study

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ABSTRACT

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Methods: We retrospectively reviewed 121 patients with OSCC treated at University Hospital Zurich. The radiologic DOI of CT, T1-weighted, and T2-weighted MRI were compared with histological DOI. Frequency of relevant imaging artifacts was assessed as well.
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Conclusion: CT and MRI measurements of DOI in OSCC lead to an overestimation of histological DOI, especially in tumors with DOI<5 mm, with upstaging by imaging in over 50 % of the cases. Artifacts were present in more than 20 % of performed images.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common cancer worldwide and the most common site of malignancy in the head and neck [1]. OSCC is primary treated by surgical resection and neck dissection or sentinel node biopsy in early stages [1]. The indication for adjuvant radiotherapy is discussed on the interdisciplinary tumor board based on histopathologic features of the specimen such as lymphovascular invasion (LVI), perineural invasion, (PNI), size of the primary tumor, close or positive margins, lymph node metastases and extranodal extension (ENE) [2,3].

Analogically to Breslow's thickness in malignant melanoma [4] of the skin, depth of invasion (DOI) of the tumor has revealed to be an important prognosticator and highly predictive for the occurrence of lymph node metastasis [5,6]. DOI is measured histologically from the basal membrane of the normal mucosa perpendicularly to the deepest portion of invasion [7]. It has been integrated into the newest 8th *Union International Contre le Cancer (UICC)*, TNM Classification for Malignant Tumors for OSCC [8].

Since it is not only relevant for staging purposes, but also in guiding appropriate surgical resection and reconstruction planning [7,9], accurate preoperative determination of DOI is mandatory. Clinical examination does not allow an accurate estimation of DOI [10]. Some authors have reported the use of intraoral ultrasound [11]. However, this

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technique is not well established throughout the world. The evaluation of oral cancer is usually performed by cross-sectional imaging, namely by computed tomography (CT) and/or magnetic resonance imaging (MRI) [12]. CT and MRI were reported to overestimate DOI by about 20–30 % [7,10,12,13] and may perform worse in superficial tumors (<5 mm DOI) [10]. Some authors have however showed that DOI is an independent prognosticator even in early tumors and that these tumors may benefit from aggressive upfront surgery [6,14].

While some have reported better accuracy of CT over MRI [15], the measurements variations specific to each modality have been only scarcely reported [10,16]. Similarly, the measurements variations specific to each DOI and how they may change between thin and thick tumors have not been thoroughly reported [10,16]. Finally, the rate of imaging-related artifacts rendering the assessment of preoperative DOI unreliable is often not mentioned in previous studies.

We hypothesized an overestimation by imaging modalities as compared to histology that would be more pronounced for MRI than for CT.

The aim of the study was to assess the accuracy of imaging-based estimation of DOI in relation with the tumor histological DOI. We also assessed the metastasis risk according to DOI.

2. Materials and methods

The STROBE Guidelines were applied to ensure adequate reporting of our research [17]. We performed a single institutional retrospective study of OSCC patients and compared histological DOI to DOI estimated by preoperative CT, T1- and T2-weighted MRI. We also analyzed how the estimated T-classification changed between preoperative imaging and histological DOI.

2.1. Study population

Patients with biopsy-proven oral squamous cell carcinoma (OSCC) treated from 2007 to 2016 at the Department of Otorhinolaryngology – Head and Neck Surgery of the University Hospital Zurich, Zurich, Switzerland with available pre-therapeutic computed tomography (CT) and/or magnetic resonance imaging (MRI) were included in the study. All patients were treated with primary surgery (wide local excision and neck dissection) followed by adjuvant radio(chemo)therapy as needed. Patients treated with induction chemotherapy, primary radiation or brachytherapy were excluded. Detailed demographic data on age, gender, comorbidities, smoking, drinking habits, clinical and pathological stage, tumor grading, depth of infiltration was obtained. Patients were staged according to the *Union Internationale Contre le Cancer (UICC)*, TNM Staging for head and neck cancer, 8th edition 2017 [18].

2.2. CT and/or MRI image acquisition

The CT images were acquired on a high-resolution Discovery VCT scanner (GE Healthcare®, Waukesha, WI, USA), using a standard, vendor-defined, and contrast enhanced protocol. No metal artifact reduction protocol was used.

All MRI imaging were performed on a 1.5-T magnet Signa HDxt (GE Healthcare®, Waukesha, WI, USA) using a dedicated eight-channel neurovascular (NV) array coil without contrast enhanced protocol (8CTL12, GE Healthcare®). The patient was in a supine position with the head immobilized with foam cushions.

2.3. Image and histological analysis

The images were reviewed by the first author (TW) and an experienced board-certified neuroradiologist (SP) and were blindly interpreted by both without knowledge of the histopathologic results. DOI was measured at the deepest infiltration point on CT images (soft tissue window, with contrast) and contrast enhanced T1-weighted and T2 weighted MRI images. The DOI was measured from the level of the mucosal surface adjacent the tumor to the deepest point of tumor invasion (Fig. 1A– C). The axial respectively coronal images were chosen according to the tumor location (axial for oral tongue, coronal for floor of mouth) [19]. The mean of both measurements by TW and SP was compared to histological DOI. In case of strong disagreement, cases were reviewed by a third person (GBM), who was also blinded of the histopathological DOI, and discussed with TW and SP. The final read was determined by consensus of all three readers

Relevant imaging artifacts such as dental light scattering, motion artifacts, and blooming were also assessed for all patients. We use a binary scaler of present/not present.

All tumor specimens were reviewed by an experienced pathologist (NJR). Histological DOI was measured from the main specimen from the wide local excision done at the time of the surgery. Measurement was done using an optical micrometer from the level of the basal membrane of the normal mucosa to the deepest portion of the tumor invasion (Fig. 1D), as previously described [7].

2.4. Statistical analysis

For descriptive statistics, absolute numbers with the relative percentage are given. For continuous variables, we report median and interquartile range (IQR). Cohen's kappa test was used to assess inter-reader agreement between the two image readers (TW and SP). Values of less than 0.20 indicates poor agreement, meanwhile, 0.2–0.4 indicate a fair agreement, 0. –0.6 a moderate agreement, 0.6–0.8 a good agreement, and 0.8–1.0 a very good agreement [20]. Correlations between continuous variables were assessed using the two-tailed Spearman rho test. Stage migration between histological DOI and preoperative imaging were performed classifying DOI according to the actual TNM classification, that is <5 mm. 5−10 mm, and >10 mm [18]. To compare distribution among non-normally distributed samples, the non-parametric Mann Whitney *U* test was used (2 samples).

A *P* value lower than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS® 25.0.0.1 software (IBM®, Armonk, NY, USA).

3. Results

3.1. Patient and tumor characteristics

A total of 121 treatment-naïve patients with OSCC with available pre-therapeutic MR/CT were included in this study (Table 1). The median age at diagnosis was 65 years (IQR 56−74.5). There was a clear male predominance with 75 (62 %) male and 46 (38 %) female patients. 51 (42.1 %) had oral tongue cancer, 41 patients (33.9 %) floor of mouth cancer, and 29 (24 %) tumors in other regions of the mouth (buccal mucosa, retromolar trigone, gum). Early T-classification (pT1-pT2) was present in 57 (47.9 %) of the patients, while 64 (52.1 %) of patients had pT3-pT4 tumors. Nodal status was positive in 44 patients (36.4 %), of which 7 (5.8 %) were staged with pN1, 28 (23.1 %) with pN2a-pN2b and 9 (7.4 %) with pN2c-pN3 categories.

3.2. Imaging characteristics

For 110 (90.9 %) patients, preoperative CT was available. For 90 (74.4 %) patients, a preoperative MRI was available. Both modalities were available for 79 patients (65.3 %).

The radiological DOI estimated by CT with contrast medium was measured in 110 patients (90.9 %) with a median of 12 mm (IQR 5.25–18.25). The T1- and T2-weighted MRI estimated DOI were available for 80 and 76 patients, a median of 11.5 mm (SD 7–17.5) and 11 mm (IQR 7–17), respectively.

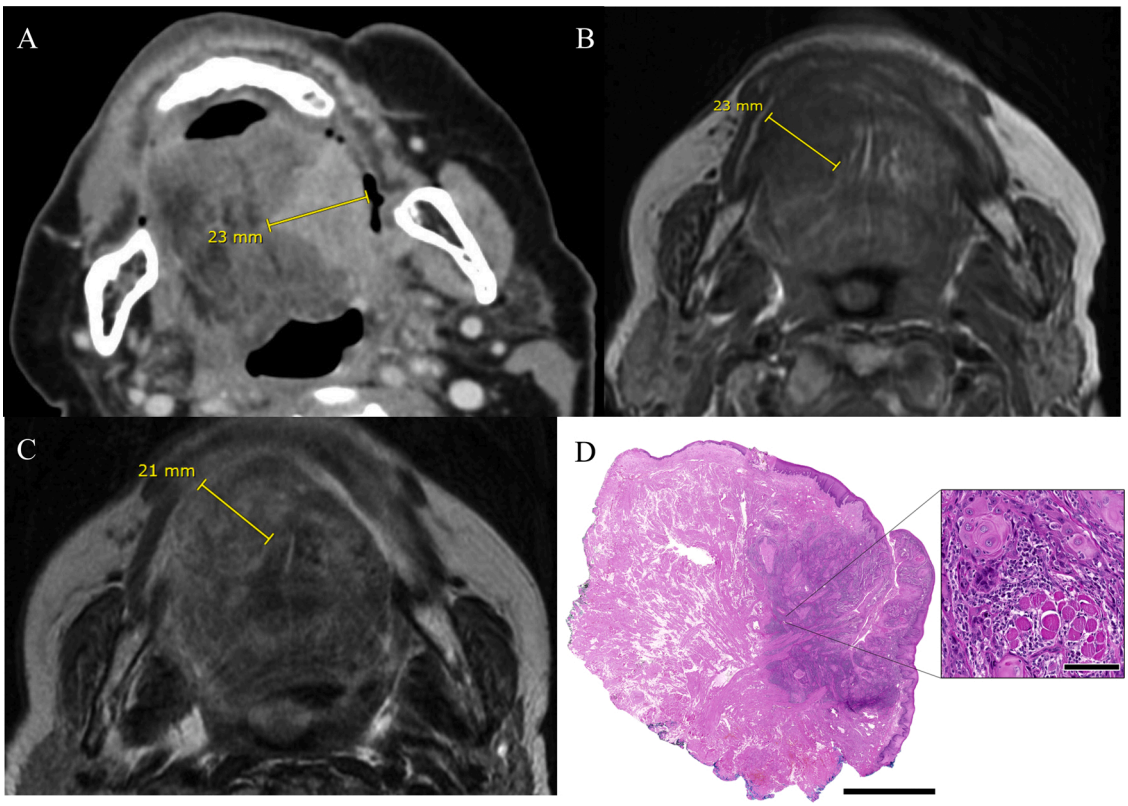

Fig. 1. A: Representative image of axial CT of oral tongue squamous cell carcinoma. The measured depth of invasion (DOI) is shown in yellow. B: Representative image of T1-weighted axial MRI of oral tongue squamous cell carcinoma. The measured depth of invasion (DOI) is shown in yellow. C: Representative image of T2-weighted axial MRI of oral tongue squamous cell carcinoma. The measured depth of invasion (DOI) is shown in yellow. D: Representative microphotography of histological depth of invasion (DOI) as measured upon histopathological examination.

3.3. Kappa inter-reader agreement

Cohen's kappa coefficient was calculated to assess inter-reader reliability and compare CT to T1-MRI and T2-MRI respectively. For CT, the inter-reader kappa coefficient was 0.638. For T1- and T2-weighted MRI, inter-reader kappa coefficients were 0.486 and 0.394, respectively.

3.4. Correlation between histological depth of invasion and cross-sectional imaging modality

We analyzed the depth of invasion as measured by definitive histopathology and as estimated by preoperative imaging. All diagnostic modalities (CT, T1-weighted MRI, and T2-weighted MRI) tended towards an overestimation of the histological DOI (Fig. 2, Panel A–C). The best correlation coefficients between histological DOI and radiological was seen for CT and T2-weighted MRI (Spearman rho test, $r = 0.718$ and $r = 0.679$, respectively; $P < 0.0001$ for both), meanwhile it was slightly inferior for T1-weighted MRI (Spearman rho test, $r = 0.635$, $P < 0.0001$).

When water-plotting mean differences between cross sectional imaging estimated DOI and histological DOI, it became evident that all imaging modalities (CT, T1-weighted MRI and T2-weighted MRI) lead to an overestimation of the DOI in thin tumors (<5 mm) (Fig. 3, Panel D–F, respectively).

This trend becomes very evident when observing the rate of T-classification migration between radiological DOI, respectively for CT, T1-weighted MRI, and T2-weighted MRI, as compared to histological DOI (Tables 2–4). All imaging modalities upstaged thin tumors (<5 mm DOI) in over 50 % of the cases. For tumor with DOI between 5 and 10 mm, both upstaging und downstaging were seen, meanwhile thick tumors were mostly staged correctly by cross-sectional imaging.

3.5. Occurrence and description of artifacts

Eighty-three patients (75.5 %) had scattering artifacts due to dental amalgam on CT imaging. Of those, scattering was so strong in 25 (22.7 %) patients that radiological DOI was not estimable.

For MRI, 18 patients (20 %) had artifacts rendering DOI not estimable (blooming in 13 patients (14.4 %), motion artifacts in 4 (4.4 %), 1 (1.1 %) with both (Fig. 3A).

3.6. Depth of invasion and lymph node metastasis risk

The lymph node metastasis risk was plotted against the histological depth of invasion, divided into three categorical groups (5 mm-categories from 0 to 15 mm) (Fig. 4). The histological DOI and lymph node metastasis risk correlated significantly (Mann Whitney *U* test, $P = 0.046$).

When assessing metastatic ratio and histological DOI, we observed a significant correlation as well (Fig. 5, Spearman rho, $P = 0.032$)

4. Discussion

The current study compares depth of invasion measured on contrast-enhanced CT, T1- and T2-weighted MRI with histological depth of invasion in a consecutive cohort of oral squamous cell cancer treated with upfront surgery. We show that both CT- and MRI- estimated depth of invasion correlated significantly with histological depth of invasion. CT and T2-weighted MRI performed slightly better than T1-weighted MRI. All modalities were however linked with a significant bias that the clinicians should be aware of during patient consenting and surgical planning. All modalities showed poor accuracy for thin tumors with depth of invasion <5 mm. Further, imaging-based depth of invasion was

Table 1
Patient demographics and clinical characteristics.

Variable		All patients No. of patients = 121	Oral Tongue No. of patients = 51	Floor of mouth No. of patients = 41	Other No. of patients = 29
Age (Years)	Median (IQR)	65 (56–74.5)	61 (54–73)	64 (55.5–71.5)	72 (66–82)
Gender					
Male	No. (%)	75 (62)	28 (23.1)	34 (28)	13 (10.7)
Female	No. (%)	46 (38)	23 (19.2)	7 (5.8)	16 (13.2)
Smoking					
Pack years	Median (IQR)	25 (0–50)	0 (0–40)	40 (27.5–60)	0 (0–27.5)
>10PY	No. (%)	69 (57)	23 (19)	35 (29)	11 (9)
<10PY	No. (%)	52 (43)	28 (23.1)	6 (5)	18 (14.9)
Alcohol					
Yes	No. (%)	49 (40.8)	15 (12.4)	24 (19.8)	10 (8.3)
No	No. (%)	71 (59.2)	36 (29.8)	17 (14)	19 (15.7)
pT-classification					
T1-T2	No. (%)	57 (47.9)	33 (27.3)	18 (14.9)	6 (4.9)
T3-T4	No. (%)	64 (52.1)	18 (14.9)	23 (19.0)	23 (19.0)
pN-classification					
N0	No. (%)	77 (63.6)	37 (30.6)	26 (21.5)	14 (11.6)
N1	No. (%)	7 (5.8)	3 (2.5)	2 (1.6)	2 (1.6)
N2a-N2b	No. (%)	28 (23.1)	7 (5.8)	9 (7.4)	12 (10
N2c-N3	No. (%)	9 (7.4)	4 (3.3)	4 (3.3)	1 (0.8)
Preoperative cross-sectional imaging					
CT	No. (%)	110 (90.9)	44 (36.4)	39 (32.2)	27 (22.3)
MR	No. (%)	90 (74.4)	38 (31.4)	32 (26.4)	20 (16.5)
CT&MR	No. (%)	79 (65.3)	31 (25.6)	30 (24.8)	18 (14.9)
Histological depth of invasion (mm)					
0–2.5	No. (%)	11 (9.1)	4 (7.8)	7 (17.1)	0 (0)
2.5–5	No. (%)	10 (8.3)	6 (11.8)	1 (2.4)	3 (10.3)
5–7.5	No. (%)	15 (12.4)	7 (13.7)	4 (9.8)	4 (13.8)
7.5–10	No. (%)	19 (15.7)	9 (17.6)	7 (17.1)	3 (10.3)
10–12.5	No. (%)	5 (4.1)	3 (60)	1 (20)	1 (20)
>12.5	No. (%)	22 (18.2)	9 (17.6)	10 (24.4)	3 (10.3)

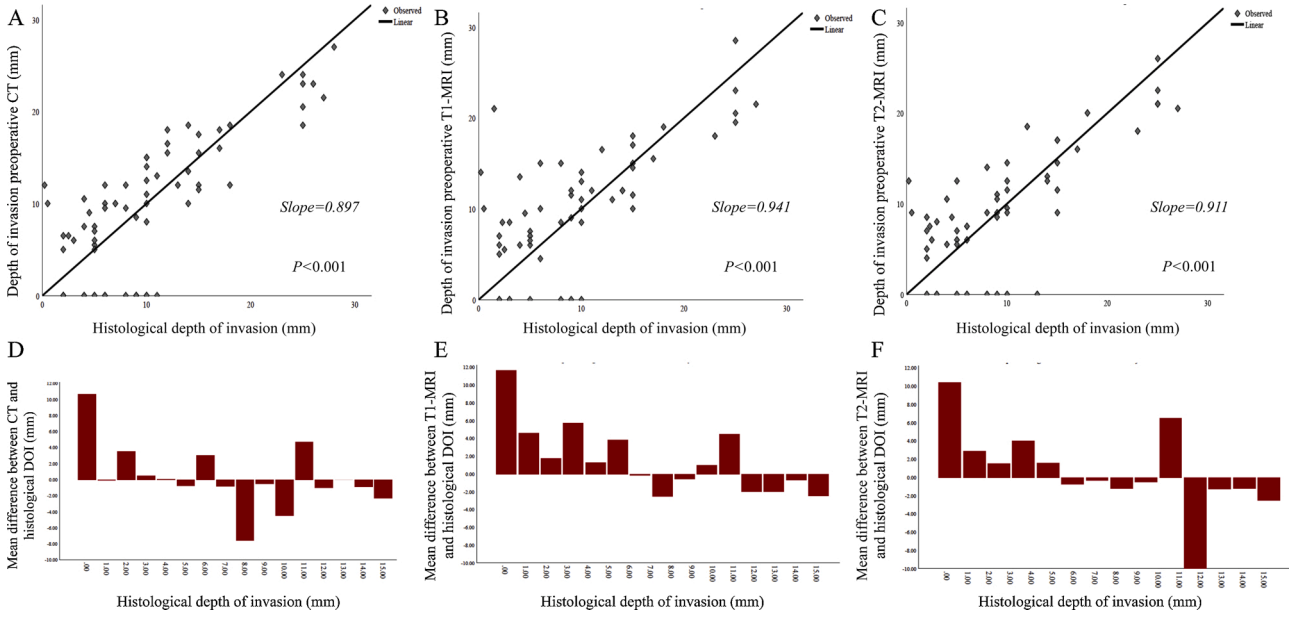

Fig. 2. A, B, C: Graphical representation of measured depth of invasion (DOI-x axis) against histological DOI (y-axis) for (A) CT, (B) T1-weighted MRI and (C) T2-weighted MRI. The respective slopes for linear curve estimation and P values are indicated for each curve. D, E, F: Water plot comparing the mean difference between the measured DOI and the histological DOI for each imaging modality (D: CT, E: T1-MRI, F: T2-MRI).

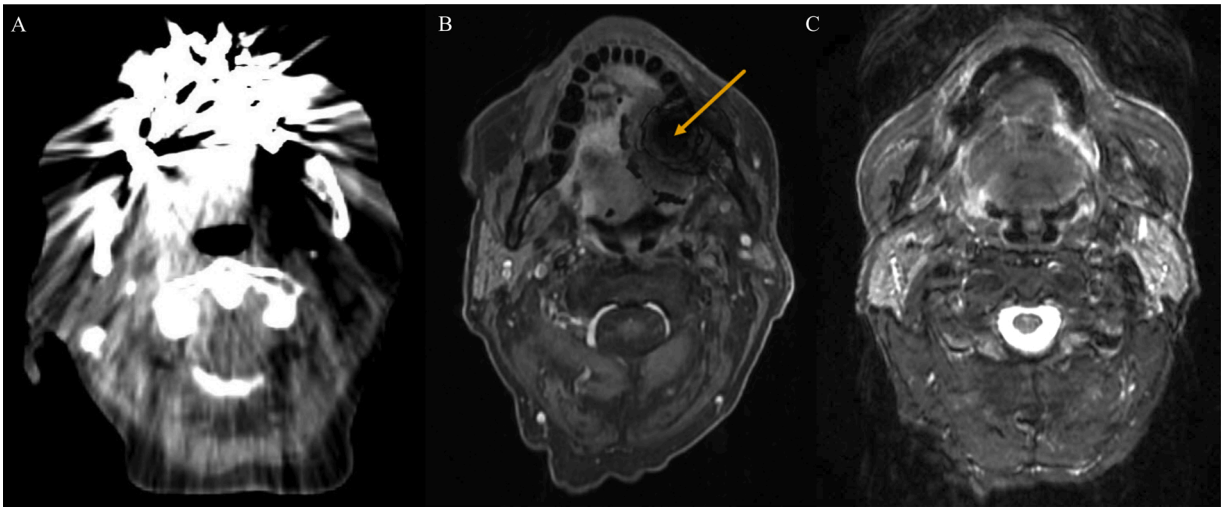

Fig. 3. Imaging artifacts: A: Representative image of axial CT demonstrating strong dental artifacts, rendering measurement of DOI impossible. B: Representative image of axial T1-weighted demonstrating blooming, rendering measurement of DOI impossible. C: Representative image of axial T2-weighted demonstrating motion artifacts, rendering measurement of DOI impossible.

Table 2
Rates of T-classification migration between histological depth of invasion and CT.

Variable	concordant %	upstaged %	downstaged %
Histological depth of invasion <5 mm	45 %	55 %	0 %
Histological depth of invasion 5–10 mm	28 %	28 %	44 %
Histological depth of invasion >10 mm	92 %	0 %	8 %

Table 3
Rates of T-classification migration between histological depth of invasion and T1-MRI.

Variable	concordant %	upstaged %	downstaged %
Histological depth of invasion <5 mm	27 %	73 %	0 %
Histological depth of invasion 5–10 mm	29 %	42 %	29 %
Histological depth of invasion >10 mm	95 %	0 %	5 %

Table 4
Rates of T-classification migration between histological depth of invasion and T2-MRI.

Variable	concordant %	upstaged %	downstaged %
Histological depth of invasion <5 mm	29 %	71 %	0 %
Histological depth of invasion 5–10 mm	44 %	33 %	22 %
Histological depth of invasion >10 mm	88 %	0 %	12 %

not estimable in about 20 % of the cases because of imaging artifacts.

In our study we show that CT had the best correlation coefficient with histological depth of invasion, closely followed by T2-weighted MRI (r = 0.718 and r = 0.679, respectively). T1-weighted MRI was slightly inferior (r = 0.635). Previous studies have reported similar correlation coefficients for CT and MRI. In a recently published study, CT performed better than MRI (r = 0.74 for CT vs. r = 0.69 and 0.66 for T1- and T2-weighted MRI, respectively) [15]. Another study from the Netherlands show somewhat better correlation coefficient for MRI (r = 0.72), although they only reported data for T1-weighted images [21]. A further study from Canada reported overall excellent agreement between CT and histological depth of invasion (r = 0.907).

A slight discrepancy between histological depth of invasion and imaging-based depth of invasion is inherent to their nature, as they are similar but not the same [7]. Histological depth of invasion is measured from the basal membrane to the deepest point of tumor infiltration [7]. Due to various specimen cutting guides, some degree of variations of the histological depth of invasion will always be apparent. Furthermore, only a small part of the whole tissue specimen is visualized on histology, potentially missing the deepest infiltration. On the other hand, imaging-based estimated depth of invasion is assessed from the mucosal surface perpendicularly to the deepest point of the tumor. As it contains a three-dimensional stack, it facilitates identification of the deepest point. For oral tongue cancer, the best accuracy is obtained by measuring depth of invasion on axial images while coronal images are more precise for floor of mouth cancer [19].

In our study, inter-observer agreement was better for CT than for MRI, which is consistent with previous reports [19,22]. In general, the agreement tends to be better between experienced readers [22]. This can explain the rather low inter-reader agreement in our study, since only one of the readers had extensive radiological experience. On the other hand, this shows that CT are easier to read and are more readily accessible to non-radiologists [22].

Overall, the depth of invasion was overestimated by imaging by about 10 %, which is comparable with previous reports [1,7,12,13,21]. A possible explanation for the general overestimation is explained by the shrinkage and distortion of the specimen from the in-situ measurement by the surgeon to final pathologic evaluation on the microscope slide, which was reported to be up to 30 % [23,24]. Interestingly, dimensions of both tumor and margins decreased between resection and pathological analysis. The major part of the decrease was thought to occur prior to formalin fixation [24]. Further some authors argued that T1-weighted images may tend to greater overestimation that T2-weighted images of depth of invasion due to inflammation or local tissue swelling if the MRI is done after tissue biopsy [25].

As shown in our water plot analysis, the overestimation however tended to be greater for thin tumors with depth of invasion < 5 mm. This is consistent with previous reports showing poor agreement in thin

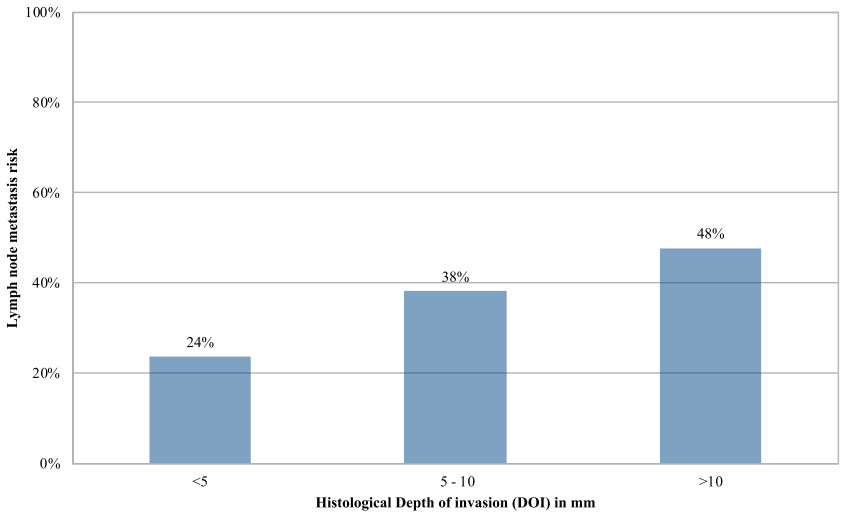

Fig. 4. Graphical representation of lymph node metastasis risk according to histological depth of invasion.

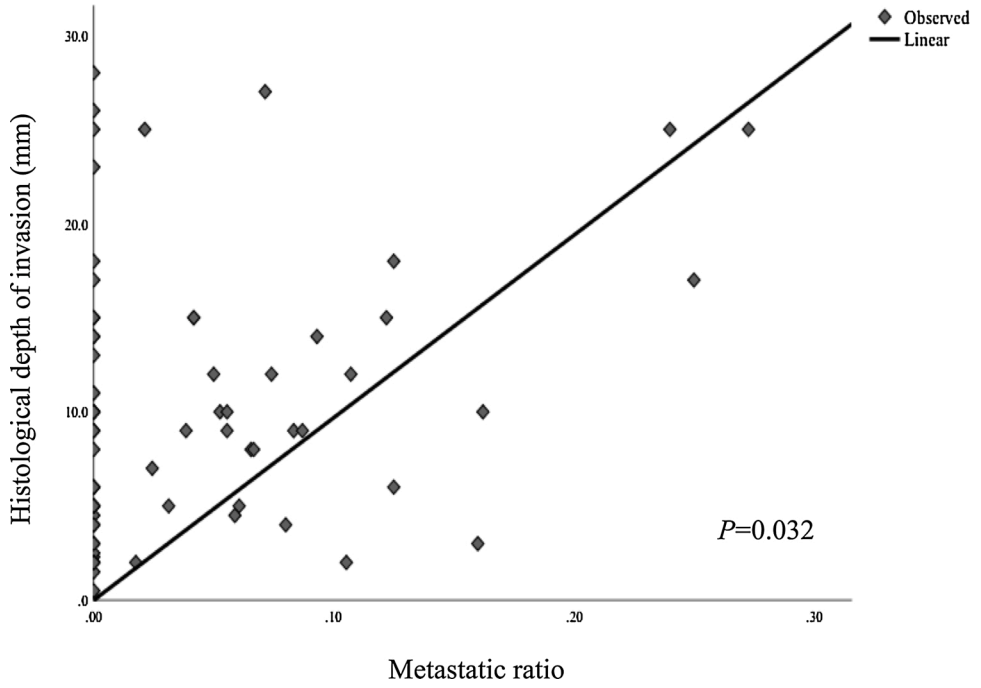

Fig. 5. Graphical representation of metastatic ratio (number of positive lymph nodes divided by total number of dissected nodes) against histological depth of invasion. The Spearman-correlation was statistically significant (P = 0.032).

tumors [10]. In early stages, this led to signification stage migration between the radiological estimated T-classification and the histological T-classification. [20]. The discrepancy shall be greater between exophytic, good differentiated tumors, meanwhile ulcerative, endophytic tumors might be dangerously underestimated by imaging-based depth of invasion. It has recently been shown that the difference in imaging-based and histological depth of invasion was greater for endophytic ulcerative tumors [25][32].

Every mm increased in depth of invasion was associated with a steady increase in metastatic risk to the neck, so the precision is required for accurate counselling and surgical planning [7]. When evaluating nodal metastasis risk in oral cancer, estimations shall be made in a continuous rather than dichotomous manner. When the latter is done using a cut-off value set at 4 or 5 mm for depth of invasion, a false idea of security may emerge for thin tumors [7]. For these reasons, pathological assessment of lymphatic drainage by sentinel lymph node biopsy or elective neck dissection remains necessary, even in thin tumors [2,6].

Preoperative estimation of depth of invasion was limited by imaging artifacts, which rendered about 20 % of all examination not accurately assessable. This is a common problem with some studies reporting over 50 % of imaging artifacts in patient with oral cancer [27]. This problem and limitation of our study may be solved in the future with e.g. metal artifact reduction software [28,29]. Another way to overcome this problem could be intraoral ultrasonography [30]. According to some authors, intraoral ultrasound could be more accurate in measuring smaller oral cancer [11,31]. Adequate ultrasound probe placement, local tenderness, and trismus are limitations to intraoral sonography [31].

Further limitations of our study are its retrospective nature and the possible measurement inaccuracies in measuring the depth of invasion on CT and MRI images. However, we used a double reader system with a third reviewer in case of discrepancy to ensure best possible

measurements quality. Further, we included cases from 2007 to 2016, which is a rather wide time range. For that reason, we could not include e.g. post contrast T1, T2 with fat saturation, or diffusion weighted imaging in our analysis. A recent study with 43 oral cancer patients reported early experience with early T1-post contrast images [22]. This may represent an opportunity for a future study. Further, technological advances and small changes in CT and MRI quality and slices thickness may have affect the measurements. However, this is a single institution study with fairly constant imaging protocols over 10 years.

In conclusion, preoperative CT and MRI measurements of depth of invasion in oral cancer lead to an overestimation of histological depth of invasion, especially in thin tumors with depth of invasion <5 mm.

Author contributions

Basic study idea by GBM. Patients search by TW and GBM. TW extracted the patients related data. CT and MRI imaging review by TW and SP. Pathology review by NJR. GBM performed statistical analysis. TW and GBM built the figures. TW wrote the first draft of the manuscript with GBM's help. Manuscript editing and review by SP, VG, NJR, MAB. TW, SP, VG, NJR, MAB und GBM have participated substantially to the study and approved the final version of the manuscript.

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Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent

Informed consent was obtained from all individual participants included in the study.

Availability of data and material

The datasets generated for this study can be obtained upon reasonable request by email to the corresponding author.

Declaration of Competing Interest

The authors have no competing interests or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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